Nash, Theodore 2018

Dr. Theodore Nash Oral History

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This is an oral history with Dr. Theodore Nash, conducted on September 24th, 2018, and on October 1, 2018, at the National Institutes of Health (NIH) about his career in the National Institute of Allergy and Infectious Diseases (NIAID). The interviewer is Dr. Victoria Harden, the Founding Director, Emerita, of the Office of NIH History and Stetten Museum.

Harden: Dr. Nash, I would ask you to begin by stating your name and that you know that this is being recorded and that you give permission for the recording.

Nash: My name is Theodore Elliott Nash, and I do give permission for this recording.

Harden: Let's begin with your birth in Miami, Florida, Miami Beach, Florida on August 30th, 1943, the second of your parents' three children. Now your parents, I believe, were Polish immigrants who must have seen economic opportunity in south Florida hotels, as did many other entrepreneurs. Would you tell me about when they came to Florida and then talk about your growing up years through high school, especially emphasizing if there was anybody who particularly inspired you to pursue a career in medicine?

Nash: My parents were young when they came to the United States. My mother [Muriel Nash], I think, was six or five. Her family came in the early 1920s. I'm not quite sure when my father [Samuel Nash] came. He was a little older, but I'm not quite sure when that occurred. They both migrated to New York, which is where they met and got married. My mother was quite young when she got married, as was usual at that time. She was just eighteen. My brother [Martin Joel Nash] came along very shortly after that.

I was between five and six years younger than my brother. I was premature, and so I spent my first few months in life at Jackson Memorial Hospital, in Miami, Florida. I was sickly as a kid, and I was very underweight. A lot of the efforts of my parents was to make me fat, at which they were never really successful. I was skinny my entire life until relatively recently.

My sister [Lori Beth Nash Dribin] came along in about 1950. At that time, my father was deathly ill and subsequently died when I was seven. My sister was just born, and luckily, the family survived. My family had moved to Miami Beach from New York supposedly because my grandmother had asthma or another lung condition, and they thought it would be better for her.

My grandfather was enterprising. He did a lot of things before he became successful. He was in the grocery business. They had a store. I shouldn't say business--it was just a store. He also was a jeweler, and I think those businesses were in New York. In Poland, he had been the owner of a dance studio. His kids were the musicians. My uncle was a concert pianist. My father was supposed to be the violinist, but he rebelled. When they came to the United States, my uncle supplied most of the money for the family to start out, because he was able to play in the movie theaters where they didn't yet have “talkies.” They had a piano player. He also played in the circuit in New York and in the Catskills

My family built a hotel, which is still present in Miami Beach. It's called the Nash Hotel on Collins between 11th and 12th Street. They eventually owned a whole series of these, maybe a half dozen, which my grandfather, uncles, and my father ran. My father was the brains of the outfit. He was the glue that held a lot of the family together. It was a devastating problem for them when he died, along with, of course, our family.

When he died, things were not looking up very much economically, but we got some money from the hotels and some money from Social Security. I had a very good childhood. I never really thought I was poor. We didn't have cars like everybody else did, but I was able to get around--buses and jitneys (which carried about 6-8 persons to specific places like Miami), and walking. Miami Beach had very good public schools. They were some of the best in Florida, so I had an excellent education. I had a lot of really good teachers.

I was always good in science. I excelled in it, and I didn't know what I really wanted to be, but my mother did. She would coach me, saying something like, "Look at those hands. Those are the hands of a doctor." I became a physician by default, as far as I know. There was no one else in my entire family who was a physician. I was quite naïve about what it entailed to become a physician and what the profession really was. I had no role model, except knowing that in the family and the culture in which I was brought up, being a physician was a thing to aspire to. Physician, lawyer, and teacher: those were the three big professions. Women became teachers and men became either doctors or lawyers. They were the career aspirations at the time I grew up.

I was accepted at Duke [Duke University], and I went there for three years. I never graduated. I went directly into University of Miami Medical School [University of Miami Leonard M. Miller School of Medicine], after my junior year.

Harden: Why was that?

Nash: Well, there were several reasons. One is that my father left me some money in his estate. This was to be used for education. I had a choice using it either for medical school or for law school. The other reason was that my brother had graduated from University of Miami and had also earned his law degree. He became a tax attorney. He was both an accountant and a CPA [Certified Public Accountant], and he was hired by the IRS [U.S. Internal Revenue Service]. They sent him first to Dallas, I think, and then to Houston. So he left Miami Beach. My mother felt that it would be good if there was a guy around to be a male presence as my sister grew up. That's one other reason I came home. The third reason is that at home, I didn't have to pay for room and board while I went to medical school.

Harden: Did the University of Miami Medical School accept people without a bachelor's degree?

Nash: Yes. There was a special program in 1963 because there were not enough doctors. There were a number of programs that accepted students at the end of the third year of college. This was a prestigious thing, and it was a good way for them to get better students, I presume. The University of Miami was a new school or relatively new school at that time.

Harden: Tell me about your time in medical school. Was there anything during this period that led you towards clinical research?

Nash: Yes, there was. I had a great time in medical school. The first few months are always like you don't really know how well you're going to do, but I excelled. I was first in my class. I got several awards for being at the top of the class. Our medical school curriculum was divided between basic science and clinical work. The first two years were basic studies. The second two years were clinical. The first two years I got those awards because I was one of the best students. I had a great education at Duke. It was harder than medical school. I really worked like a dog.

Harden: What was your major at Duke?

Nash: My major was chemistry, but I also took a lot of different courses. As a matter of fact, I was accepted to medical school early in my junior year, although I did not begin until after my junior year. When I was accepted, I dropped all the courses that I didn't have to take. I took history and all the other things that I wanted to learn. I loved history; I loved a lot of things that it would have been hard to make time for while completing a scientific major. I spent a huge amount of time in the library reading everything I could get my hands on, things that I liked, such as Egyptian history. I remember I was studying hieroglyphics at one time. When I checked out one book, it turned out that I was the only person who ever had taken out this book on hieroglyphics. I had these ideas about learning things, and I always loved learning. That was one of the few times in which I could do anything I wanted at Duke, except for my mandatory classes.

Medical school was also good. I did very well academically, and I also did very well clinically. Every summer, I did a project. My first project was with Dietrich [Dr. L. S. Dietrich]. He was doing biochemistry and NAD [nicotinamide adenine dinucleotide] synthesis. He was a major force apparently in that line. I had only a rudimentary understanding of what they were doing, and it was only six or seven weeks, but I got an idea of what research was. It was very tedious, but I was enamored by the idea that by your wits, you could learn new information, which really is something that is not obvious, I think, to everyone. The year after that, I became interested in neurology; well, I was always interested in neurology.

Harden: Why?

Nash: First of all, my father died of some neurological disease that they never really understood. He was in a coma for five months and then eventually died. I think it was something infectious. I think it was more like a chronic herpes or one of the things that nowadays would probably be a cinch to diagnose, but at that time, it lingered on and he died. That was maybe something, but I liked the idea of neuro--neurosurgery, neurology--so I went to the head of neurology, a guy by the name of Peritz Scheinberg [Dr. Peritz Scheinberg]. The University of Miami Medical School had a very good neurology department. By that time, I was reading some interesting science papers, and decided that I might study the nervous system of hydras, because of one of his papers that I read on diffuse nerve connections, which became much more current much later on. Dr. Scheinberg looked at me, however, and he was very perturbed by this idea. He said, "If you want to study the nerves of hydra, why are you coming to me?" He was quite stern, and I was really taken aback.

I started working instead with a mentor who was doing renal disease, Bill Hulet [Dr. William Henry Hulet] was his name. I became really good at renal disease. I did a research project for him on renin. Renin converts angiotensinogen to the hormone angiotensin, which is a major cause of high blood pressure, particularly in renal disease. Also, now there are medicines that are blocking the angiotensin receptors, valsartan, for instance, and all the current medicines are based on inhibiting this pathway.

I started working on that, and although I didn't get a publication from it, there were some data that were actually useful, at least to him. I worked every Saturday for an entire winter--or two years--doing that. It served me quite well, because he liked what I was doing. I worked hard, and I became really good at it.

During that time, someone from Vanderbilt [Vanderbilt University] came who was working on aldosterone. He was an endocrinologist. Fishman [Dr. Lawrence M. Fishman] was his name. He turned out to be a very close friend of Shelly Wolff [Dr. Sheldon M. Wolff], Chief, at that time of the NIAID Laboratory of Clinical Investigation [LCI] and whose lab I joined. Dr. Fishman wrote a recommendation for me, and I presumed that it was a really good recommendation, since I was accepted to that program. I was rejected by a program in renal disease, which was my interest.

Harden: What year are we talking about now?

Nash: Well, this was ’67 or '68.

Harden: But you hadn't done your internship and residency yet.

Nash: No, I had not. You had to apply for a position at NIH before completing your medical training. Just to step back a little, this was the time of the Vietnamese War. Having never shot a gun and never having been interested in shooting a gun or being shot at, for that matter, I, like many others, explored several ways of not going into the military. I applied for deferment from both the Navy and NIH. I applied for them before I went to internship. There were recommendations one needed and forms to fill out and explanations of what your interests were.

I always was an imaginative thinker, and I had this novel idea. I was interested in chronic pelvic inflammatory disease and chronic respiratory disease because I had been on a ward where there must have been 50 women who had pelvic inflammatory disease. Their physicians were harvesting pus from their fallopian tubes without growing anything. I thought that was the oddest thing that I had ever heard. Nobody knew anything about it, so I went to the library, looked for pelvic inflammatory disease, and found one paper in the entire literature for that year. I thought that this condition might be a chronic infectious disease, so I wrote up the situation and my thoughts about it for my little treatise. They must have liked it, and I'm pretty sure I had very good recommendations. At any rate, I was accepted, but I came to NIH primarily because of Shelly Wolff. It was very hard to get in here.

Harden: Yes, it was. But before we get there in this oral history, would you talk about your internship and residency? You went back to Duke for them. Was there anything special that you want to talk about during those years?

Nash: The Duke program was also prestigious and hard to get into. The reason I got in there, I think, is that there had already been one guy from the University of Miami who got into that program the year before. Nobody from the University of Miami had ever gone to that program--actually, that's not true. There had been two people who got into the program. They did very well. There were a few prestigious universities on the upward career route, and everybody tried to go to one of these. For someone from an outside university medical school, it was very hard to get into these desirable internship and residency programs. And with respect to being accepted in the NIH Clinical Associates program, almost everybody at NIH came from Yale, Harvard, Stanford, Washington University--named universities that had big research programs. It was very hard for places like the University of Miami, which were not very prestigious and had very young research programs, to get people to these places. Subsequently this changed as more and more medical schools became research competent and more established. Once you were at NIH, if you wanted to be an academic physician, you went back to one of these prestigious medical programs. Now, the entire environment and academic research has changed.

At any rate, I ended up at Duke, and I have to say it was a very hard program. The program essentially demanded that you work all the time. My faculty advisor was a guy by the name of Gene Stead [Dr. Eugene A. Stead]. Gene Stead was the foremost chairman of medicine in the United States. He was one of the most well-known, hard-nosed guys. He had made the Department of Medicine at Duke into the powerhouse that it became and it still is. But he was a very ornery guy, I have to say. The second I got there, he retired. He retired July 1st, 1968. He was not even 65. The deanship was taken over by a future NIH director, James Wyngaarden [Dr. James B. Wyngaarden], who was chairman of the Department of Medicine when I arrived. Duke had a very stringent program. We worked seven days a week. Your only time off was one night on a week day and after 12:00 noon on a weekend.

Harden: Wow.

Nash: Most of the time, we didn't take that time, because you were the only person who was allowed to write orders on the patient. If your patient was sick, you didn't leave. You just took care of that patient. You didn't have to take leave. You didn't have to take other patients, but you had to take care of that patient. That was a very common thing for us at Duke. Needless to say, during the whole year, half the time, you felt like you didn't know what you were doing. I remember that my first rotation was in neurology. This was the last week in June of 1968. I had 30 patients in neurology, and they were constantly paging me about these patients. I used to say they were paging me about patients I didn't know, about diseases I'd never heard of and that I didn't know how to treat. It was like a comedy of errors. I was constantly trying to figure out what to do. Of course, I had a resident who was trying to teach me what to do, and the nurses were teaching me what to do. This was all about survival.

Then Duke had its own way of doing things. All the charts--after a patient was discharged, they would check to see whether you did all the things that you're supposed to have done. A lot of times I didn't quite get it all done--or didn't know what to do is mostly what happened. I had to defend myself, and I actually had to call the patient back and do all the things that I hadn’t done or write all the things I hadn’t written.

At any rate, I caught on eventually. I always thought I was slow, but eventually I did pretty well, making fairly good diagnoses. It took about a half year to figure out what was going on. You could handle anything at the end of a year, at the end of internship. But you were constantly sleep deprived. Sometimes you had six or seven patients a night, and you were up all night, and the next day you had to try to catch up, write the histories, and everything else.

Harden: But you didn't spend the whole year on neurology, did you?

Nash: There were many rotations. There were some specialty rotations, not all of them. But there was neurology, there was private medicine. There was cardiology, intensive care—no, intensive cardiology, because they didn't have intensive care yet, so we took care of the really sick patients out on the ward. It was the old-time ward. They had big rooms with lots of patients, and curtains would be separating the patients. These were public wards. Medicaid, Medicare was just coming up. Most of these patients couldn't pay for their care. Duke paid for most of the care. They had a program in which they would pay for the patient. Our training was mostly on the public patients. There was a private section in the hospital, but it was not very intensive, as intensive as the public ones. I have to tell you though, the public patients got reasonable care for that time. There was not one person at Duke who didn't became a really good physician. You had a lot of confidence after that year. At the end of the year, I became a resident. We were all doing pretty well. By that time, we were seasoned veterans, so to speak.

The worst time of the year of internship was the 1968 flu epidemic. That was really bad. Half of us took off five days at Christmas, and half of us took off five days for New Years. I happen to be Jewish, so I always took Christmas duty. I was there during Christmas, when the flu epidemic was at its worst. People were being admitted and were dying right there. There were women dying--pregnant women are particularly susceptible. We had people who were immunosuppressed, lymphomas, leukemias coming in, and there were only half of us there. I was up literally for a week straight, five days. I got sick also.

Harden: Were the flu shots being given at that time to prevent flu or no? I don't remember.

Nash: I don't remember, either. I don't think they were.

Harden: That meant that all of you all working in healthcare--nurses, doctors--were quite susceptible.

Nash: Right. I was sick, but I was not deathly sick. Normally you would stay home and you would not infect your patients. But it was pretty bad. At the end of five days, the administration decided that the people who had worked over Christmas would stay and not have vacation and would work the wards, because they were short-staffed. Well, we were so strung out that none of us could work. We were just hanging out. It was like a revolt. People started quitting. Finally, the administration changed their minds. They called in the staff after that. It was really enlightening as to what happens when people are at the end of what they can do. But we survived all that. It was a great learning experience, except that I almost died doing it. I lost 20 pounds. I remember I went down to 132 pounds at my skinniest.

Harden: And you're tall. You must have been emaciated.

Nash: This internship gave us the confidence that we could do anything. Any time something interesting came up, someone would say, "Come on and see this patient." We all would trot over to see some patient who had some unusual medical condition.

Harden: You clearly enjoyed caring for patients, which you still do. I'd like to ask you a question that I pose to every physician. Why did you decide to go into clinical research, as opposed to private practice or public health?

Nash: Well, part of that is I like the idea of knowledge, of gaining knowledge. I already had learned in medical school that this was a high. The way I explain it is sort of like painting the Mona Lisa, except Mona Lisa is art, and you look at it as an original way of doing something. The same thing happens in research. Just by your thoughts, just by your ingenuity, just by doing something, you produce something from nothing--new knowledge. That is what you work for in science. That is the thing.

There is a saying in scientific research: You have your good days and your bad months. That's exactly correct. It is the most frustrating work to do, because most of the things you try don't work, or at least don't work initially for sure. You have to work like a dog, and you have to have the perseverance to do that. There are a lot of physicians whom I've trained, and I've seen that it's not in their makeup to do that. They don't persevere. They can't do it. They're not capable of doing it.

As we train people in research, one of the things that they have to learn is, "Is this stuff is right for me? Is this working like a dog, going and coming in all hours, being original, doing all the things that you have to do in order to be successful, can I do it and do I want to do it?" That was one of the things that I thought about early on and realized that, yes, this was what I wanted to do. Of course, there were also my mentors.

I was accepted into the NIH program in July of '68. I was in the middle of this horrible neurology rotation, in which I didn't know anything and was running around trying to learn neurology--which I actually never did. I got accepted into the NIH program, so during my internship, I knew that I had the NIH program coming up, I knew where I was going.

Harden: You arrived at NIH in 1970. Tell me who was in the lab at that time, about the different people in the lab, whom you worked with, and what you got started on.

Nash: The organization of the place where I worked was different than it is now. At that time, the Laboratory of Clinical Investigation was headed by Sheldon Wolff, Shelly Wolff. Shelly Wolff was a real original, and I'm sorry that almost nobody knows who he is.

Harden: There are a lot of people who do.

Nash: There is a room named after him. He's probably best known now, or at least I know him best as the mentor for Tony Fauci [Dr. Anthony S. Fauci]. He was Tony's mentor. When I came there, the prior decade had mostly been spent studying bugs. Shelly turned the place around to study the host. This was a time when immunology was being developed, and many notable, very important immunologists were here--Benacerraf [Dr. Baruj Benacerraf] was here, future Nobel Prize winner. Ira Green [Dr. Ira Green] was here. They weren't in the LCI. They were in immunology labs. Our group had about 15 PIs [Principal Investigators]. Jack Bennett [Dr. John E. Bennett] was one of the persons here. He was working on fungal disease. He was one of the few who was actually working on a bug. There was a virology lab, and that was headed by Ray Dolin [Dr. Raphael Dolin] was here or about to be here. There was Herb Reynolds [Dr. Herbert Y. Reynolds], who was working on lung disease. Chuck Kirkpatrick [Dr. Charles Harvey Kirkpatrick] was working on immune deficiency diseases. There was John Sheagren [Dr. John Sheagren], who was working in immunology. I'm not remembering everybody. There were a whole series of guys. There was a macrophage person, but I'm not remembering his name. He became very important. There were a whole bunch of white-cell guys. Shelly was interested in fever. He had a bunch of guys working in fever and periodic fever.

We had 60 beds in the ward, a lot more than we have now. There were a lot of disciplines, a lot of things that were being studied—a little bit of everything, more or less. There was parasitology. My future boss, Frank Neva [Dr. Frank A. Neva], had been hired the year before from Harvard. He was a professor at Harvard, had a named chair, and he was seduced to come here. He had worked in the school of tropical medicine. The head of that department was Tom Weller [Dr. Thomas H. Weller], who was another Nobel Laureate. Frank was a tropical medicine guy and a virologist. He was the co-discoverer of rubella and other viruses. He came here to make his mark on the Laboratory Parasitic Diseases [LPD]. He was hired by a guy by the name of John Seal [Dr. John R. Seal]. John Seal was a guy who made his fame working on cholera in Dacca [now called Dhaka, Bangladesh]. John was also an original guy. He was the NIAID Scientific Director, and he basically called the shots on everything. You didn't have to go through committees to be hired. He did the whole deal.

When I came here, the program was structured so that you had to be on the wards and get the ward experiences. We were also doing consults on infectious disease. Then we would choose a lab to go to for research work. I just remember very distinctly, I was going to go to a lab headed by John Sheagren, who was working on sarcoid and a few macrophage problems. But the problem with him was that although he was a very smart guy, he rarely saw his patients. He came late to see his patients. He would admit a sarcoid, let's say, or some sort of a patient that he was in charge of. He would mosey on over about two days later. I thought that was really bad form.

What I became interested in were granulomas. We had a lot of patients with granuloma sarcoid, granulomatous hepatitis. I was very interested in this. Frank Neva showed up in September of '68, and he had been doing a project in South America on either Chagas disease or leishmaniasis, I can't remember which. He came on the rounds, introducing himself. He was a very nice guy, and he asked, "What are you interested in?" I tell him I'm interested in granulomas. He says to me, "If you're interested in granulomas, you should be studying schistosomiasis," because there is this model of schistosomiasis and granulomas. That was a segue into parasitology. I didn't know much about parasitology at all. He sort of seduced me to do this project on granulomas. Subsequently, unfortunately, when I went ahead to do a project on granulomas, no immunologist in the entire NIH would work with me because they didn't like parasitology. The field of parasitology was like a pariah. It was old parasitology. It was not keeping up. They didn't do the hard biochemistry, or at least very few people did. It was very descriptive, very biologic. It didn't have a really good reputation, and, of course, that's one of the reasons they hired this guy from Harvard to come here and fix things up, which he subsequently did. In just a few years, he remade the laboratory into a laboratory second to none.

Harden: When you first got into schistosomiasis, you went to Brazil to work with the Pan American Health Organization. I want you to tell me what you did there. But could you also, as we get started, explain what schistosomiasis is?

Nash: Well, as I was saying, there was a granuloma schistosomiasis model developed by a guy by the name of Franz von Lichtenberg [Dr. Franz von Lichtenberg] at Harvard. In this model, they injected schistosome eggs into the lungs of mice, and the mice developed a granuloma around the egg, and they could manipulate the system. They could make it bigger or smaller, using different steroids and to find out what a granuloma is by that system.

Frank Neva didn't know a lot about schistosomes. He knew about the disease, but he didn't know many details about the organism. But there was a guy who did, who became my immediate boss. His name was Allen Cheever [Dr. Allen W. Cheever]. Allen had also been a student at Harvard Medical School. In medical school, he had worked with Tom Weller on schistosomes. Allen was a pathologist who became an expert on model infections of schistosomiasis in animals.

Schistosomiasis is a major disease of the third world. There are several varieties of it, but two are most common. One is intestinal schistosomiasis and the other is urinary system schistosomiasis. You get schistosomiasis by wading into fresh water, in which snails, which are the intermediate host, live. They release the infective form of the organism called cercariae. Cercariae burrow through the skin and make their way to the lung over a month and then into the blood vessels. Then they end up in the venules of the intestine, mostly in the large intestine but some in the small intestine. The ones that up in the urinary system are the variety called *Schistosoma haematobium*.

The intestinal varieties come in two varieties. One is *Schistosoma mansoni,* which is present in South America and Africa by and large. *Schistosoma japonicum*, which is present in the far east, was present in Japan initially, and that is where the life cycle was described. It is still a major problem in China, the Philippines and other areas. There are also other minor species.

Schistosome worms end up in the blood vessels, and unlike other trematodes, there's a male and a female, and they pair up in the blood vessels, and they have suckers. They crawl around the vessels, and they lay eggs. These eggs do two things. Some are extruded into the tissue. If they're in the bowel, they go into the tissue and they form granulomas—each egg does. Some of the eggs may be swept back into the liver or other organs. When they're swept back into the liver, if this happens for a long period of time, you get liver disease. It becomes a plumbing issue. Patients get portal hypertension or they die from esophageal varices and bleeding. This is the major mortal complication of schistosomes.

1. *haematobium* goes to the urinary bladder, and there they cause lesions in the bladder and the ureter, they can cause renal failure from obstruction of the ureters. They also cause inflammation within the bladder so you get cystitis, a type of cystitis and hematuria and infections. There are a whole series of associated diseases. The other major complication there is bladder cancer. It's a precursor of a certain type of

bladder cancer, which is really common in the developed world. Schistosomiasis was brought to the Americas via the slave trade. It's now endemic in Brazil, in some parts of Venezuela, and in the Caribbean. It was a really important disease in Puerto Rico. It was basically first studied by United States investigators and the NIH in the '30s. It was a major problem in Puerto Rico. It's been eradicated from Puerto Rico now, but when I came on the scene, it was still present in Puerto Rico. They were still having epidemics of the initial infection, which is called acute schistosomiasis, which I became involved in.

Harden: But you went first to Brazil.

Nash: No. I first went to the lab. Then what happened was interesting. Frank Neva gave me a project, which was a duplication of a project that Tom Weller, the Nobel Laureate, was doing. In a way, Tom Weller and Frank Neva, they were competitors. They had a love-hate relationship in some way, as far as I can tell. Frank never talked about Tom Weller. He never said anything bad about anybody, but I got the sense that this competition was the reason he gave me this project. Later we can get to the definition of a circulating antigen in schistosomiasis. Tom Weller had thought about it initially and was developing an approach to isolate it, but he didn't get the answer. I did. That is why I was able to stay at NIH--because of this project.

Meanwhile, the first year that I worked on this project, I got nowhere. I couldn't duplicate the published study done by the Harvard group, despite how many hours that I put in. I spent a lot of time doing things that didn't pan out. Everybody was frustrated, including myself, to the point that I thought I was going to leave NIH and go into private medicine, because things here weren't going well.

Frank decided that it might help if I went to Brazil to learn more about the disease. I saw a disease here, and I saw a lot of cases, but it's really different in an area with endemic disease. I went to Brazil, and they groomed me for studying this disease. At PAHO [Pan American Health Organization] one of the major guys there was named Louie Olivier [Dr. Louis J. Olivier]. Louie Oliver used to work in schisto at NIH. PAHO paid for my trip to Brazil to spend two or three months there doing a study with a guy by the name of Kurt Kloetzel [Dr. Kurt Kloetzel]. Kurt Kloetzel was a brilliant investigator but a loner and a bizarre person. He discovered and wrote up the specific epidemiology of schisto. He had an idea of treating patients who had a lot of disease. One of his major goals was to prove that if a patient had a lot of these parasites, the patient had a propensity to develop liver disease; the risk was very high. There was a measure of liver disease, of high burden parasites, by looking at the stool and seeing how many eggs you had. There was a big deal about quantification of infection, which is one of the reasons I was working on this antigen. We hoped that the circulating antigen would serve to provide a measure of how many worms a patient had, which was also a measure of whether the patient would get bad liver disease. Kurt Kloetzel also believed that if you treated these patients with a drug, that you could prevent this liver disease. That was what I went down to Brazil to do.

Kurt had already defined the epidemiology of schisto, when you develop liver disease, when you develop a bad spleen, when you started bleeding, what was going on in the temporal way. He did this all by himself. After he graduated medical school, they sent him out to the boonies to do a project that was the school's service to these people. Being very enterprising and very smart, when he was sent to this town that had a huge amount of schistosomiasis, he put everything together: He put the clinical stuff and the epidemiology and where the worms were, where the infection was, where the snails were, what the clinical thing was. He put that all together.

I was going to work with the master, so to speak. But meanwhile, I had been getting nowhere in my project. I made some advances. The major problem was that I wasn't able to develop antibodies to this antigen that was defined in a certain way. It turned out that natural infections produce a lot of this antibody. I was able to use human and animal sera infected with schistosomasis as a source of antibodies to this antigen that allowed detection and purification and in particular studies to define the characteristics of the antigen. That was sort of the key to defining this antigen, because I had an assay to it. Monte Bawden [Dr. Monte P. Bawden] at Harvard, who was doing this similar project, found a way to make antibodies. He told me how to do it. The secret was to combine mixture of antigens from the worms with methylated BSA [*bovine serum albumin]*. I was now making antibodies in rabbits. That was the secret to doing it. That was the key. I did a paper on defining what this antigen was. It turned to be a proteoglycan.

Using these antibodies, I was able to find that there was this proteoglycan in mice. That was my first *Journal of Immunology* paper. It was hard to get into the *Journal of Immunology* at that time. The paper defined the nature of the antigen and how to purify it. It was mostly a carbohydrate with some peptides or a proteoglycan. Prior to that it was unclear what it was, and the best suggestion from the original report (Berggren and Weller, 1967) was that it was DNA. I showed that it was a proteoglycan, the first of a number of parasite antigens that one could detect in body fluids. This antigen was one of the first, if not the first, defined antigen in schistosomiasis or in any other parasitic disease. It was a big deal.

The second paper had to do with localizing the antigen in the worm. It turned out to be a worm gut antigen. Schistosomes are odd parasites, but all the trematodes have one thing in common. They don't have an anus, but they do have a mouth. What they do is take in serum and red cells, they digest the things, and then they spew it out. This is an intervascular spewing out. All these worms are in the vessels. They're in your blood stream, and you could have a thousand of them. People have counted them, and you could have thousands, 3,000, 5,000 worms, although these numbers are high, usually there are many fewer. All of these worms are taking in stuff and spewing it out. Some of the stuff they spew out happens to be their gut contents, which includes one of these antigens.

That's what we were measuring. I put that story together. That's what I did when I left NIH in 1974. I left for two reasons. One, I was already trained in infectious disease. When I left NIH, I was the attending physician at the Naval Hospital [National Naval Medical Center, Bethesda, MD] in infectious disease, but I didn't think I knew enough. So I got a fellowship at Harvard to do infectious disease. It was the Beth Israel Children's Hospital Fellowship program. That's where I went. That was the first year. The second year, I did training in carbohydrate chemistry in a lab headed by Roger Jeanloz [Dr. Roger W. Jeanloz], who was the discoverer of amino sugars. He was a chemist. I worked in that lab to define what this antigen that had carbohydrates in it and protein was. I worked with a fellow [postdoctoral fellow] who was helping me there, Nasir-Ud-Din [Dr. Nasir-Ud-Din].

We had the most fun you could possibly imagine, both of us. It was a great time. Boston was great because of the training and who was there. After two years, I was ready to come back. I came back in '76, so I had spent two years, one doing the ID [Infectious Diseases] fellowship and the other one doing the fellowship in what was called biological chemistry.

Harden: You arrived back at NIH in 1976, when Frank Neva was reorganizing the lab. Would you talk about staff changes at this point? Who left? Who stayed? What changes in focus were there?

Nash: Frank's reorganization had a lot to do with why I stayed and why I was able to stay. The lab at that time, the Laboratory of Parasitic Diseases (LPD), was composed of a people who worked in disparate geographic areas. Part of the lab was in Hawaii [Pacific Research Section]. It was headed by Leon Rosen [Dr. Leon Rosen], a virologist. He headed a small group that did parasitology and virology in the South Pacific. Then there was a group in Chamblee, Georgia, that was doing human volunteer studies in Malaria [Primate Malaria Section]. Then there was the lab at the NIH.

One of the first things that happened is that some people were fired or let go for one reason or another. Sometimes they didn't like what they were doing. Sometimes they had personality issues, whatever. As you know, you don't get tenured immediately at NIH. These people knew that they were in a temporary position. When I first came here, for example, before Frank Neva came, Allen Cheever was the temporary chief, acting chief. He hired some people who may still have been in temporary status.

The lab was consolidated. The people in Hawaii were given, not their marching orders, but given a time limit in which they had to finish up and go somewhere. They were given some money to go, and they stayed in Hawaii, but under a different institution. They're at the university, but they were no longer part of the LPD.

The Chamblee unit was closed. It became unfavorable to do any human prisoner volunteer work. The malaria people stayed at the CDC [U.S. Centers for Disease Control and Prevention]. One of them was Bill Collins [Dr. William E. Collins], and there were a few others. The fellow came up here. The fellow there was a guy by the name of Dave Wyler [Dr. David J. Wyler]. He was of my stature at the time, a fellow. He came to NIH trying to get a lab and do work.

All this consolidation freed up slots for positions that Frank could play with to hire people. The most important thing that he did was to hire a guy by the name of Lou Miller [Dr. Louis H. Miller]. At one point in 1971, Frank Neva, I remember, went up to Columbia for a weekend. When he came back, I met him in the hall. I said, "Frank, what happened? What'd you do?" He said, "I hired this guy, Lou Miller." He further explained that he was the only guy who had new ideas about malaria. Of course, going forward, Lou developed his malaria lab into a powerhouse. When I came back in '76, he already had a major paper in *Science*, I think it was, on the invasion of the merozoite in red cells, working with a guy by the name of Jim Dvorak [Dr. James Dvorak], who was in our lab. Jim was working on Chagas disease. I should say that when I came here, the people in the LPD included, of course, Allen Cheever, who was working on schistosomiasis, and Jim Dvorak, who was not quite tenured, working on Chagas.

They also had a big toxoplasmosis lab, and just the year before I came here, the life cycle of toxo was described by two people simultaneously, one at NIH here in LPD. I'm trying to remember his name. Harley Sheffield [Dr. Harley G. Sheffield], that is who it was. Leon Jacobs [Dr. Leon Jacobs] had already gone to the head office to become, I think, associate director or something of NIH, of NIAID I think, or the Fogarty Center [Dr. Jacobs held senior positions in each component]. I can't remember. But toxo was still very big, and LPD had a group researching it. There was also an amoeba group headed by a guy by the name of Louis Diamond [Dr. Louis S. Diamond]. "Buddy" Diamond was what we called him.

Theresa Mercado [Dr. Teresa I. Mercado] was a woman investigator who was doing biochemistry, not well, but trying to do it. She was hired by one of the prior lab chiefs to help. Gene Weinbach [Dr. Eugene C. Weinbach**]** was working on mitochondria and energy metabolism and found that some protozoan organisms didn't have any. He defined how their energy metabolism was performed if they didn't have mitochondria.

There were a few other people in the malaria lab, but Lou eventually got rid of them or made it advantageous for them to leave--I'll put it that way. I'm not quite sure what the politics were, but they eventually left. They were from the old school doing malaria research.

There was a guy by the name of Bill Pacheco [Dr. Guillermo Pacheco] who was working on filaria. Bill was really well trained and a really nice guy doing filaria. He was feeling ill, so the story goes, when one day a fellow working with him--one of my comrades—did a blood smear on him and diagnosed acute leukemia in him.

Harden: Wow.

Nash: Bill subsequently became a patient here and went through a bone marrow transplant and died. As it turned out, his position in LPD is the one that Frank Neva was able to put me in. If Bill hadn't died, I'm not quite sure I would be here. It was really very sad. He was quite young. He was, I think, in his 40s, maybe early 50s. He was a young, dynamic guy, and a really nice guy. He trained at Tulane. He was initially from, I think, Colombia, South America.

At any rate, these were the people who were in LPD when I first came here. Except for me, there's no one living in all that group anymore.

Harden: Let's come back to schistosomiasis. I want you to walk me through the research on the circulating antigen for diagnosis and quantification.

Nash: So my first research had to do with schistosomiasis. As I explained, I worked under Allen Cheever, and Allen was a wonderful guy. Between him and Frank Neva, I couldn't imagine being in a better place and having better mentors. They were both wonderful people and very good scientists. But Allen, who was a pathologist, was, in my mind, not quite keeping up with the times. He was really good at developing model systems. He was infecting every monkey in sight as a model for schisto, plus a whole bunch of other animals. He was a biologist using microscopy techniques and stool examinations. That was really his forte; he understood the biology of what was going on in schistosomiasis. I learned everything from him. He was encyclopedic. He had a copy of almost every paper written on schisto up to that point, and I read almost every one of them. He was extremely supportive, and he always edited my papers. I was a horrible writer. He would edit everything. He was really very helpful.

Frank, however, had given me the project of defining this circulating antigen and basically reproducing what was done at Harvard. As I said, it was hard sledding, because I couldn't produce an assay to find it. I finally did, and then using that assay, I was able to purify it. Now there was another player here who was really helpful. His name was Ben Prescott [Dr. Benjamin Prescott]. Ben was trained at Rockefeller [Rockefeller University] before he came to NIH. His bag was carbohydrates. He was a very early carbohydrate chemist. He was working on pneumococcal vaccines. He actually developed the methodology for producing the first pneumococcal vaccine. That entailed taking pneumococcus, extracting the cell wall from the pneumococcus bacterium, and using it to make the vaccine.

I did one critical experiment. One of the techniques I was using at that time was electrophoresis in agar. I was staining the agar, and I was getting signal from the antibody, but I was getting nothing else from it. I was using some very primitive experiments to determine its characteristics using solubilities, size determination, heat and oxidation effects etc. One of them was trichloroacetic acid [TCA]. Everything not acidic precipitates when you add the stuff and the antigen remains soluble in solution, suggesting it is not a protein. It was a way of getting rid of protein. I got rid of the protein, and I saw that the antigen was still soluble. This suggested that the antigen wasn't a protein.

At any rate, for all of the techniques and other things that I didn't know anything about, I went to Ben Prescott. He told me how to do the purification and how to use TCA. His expertise proved to be integral to defining the fact that this antigen was not a protein. It was mostly carbohydrate. That was why I then went to Harvard, because they were carbohydrate chemists. They were able to tell me about carbohydrates and how you analyze them.

The first paper was defining the antigen. I named it GASP for gut-associated proteoglycan. Later, when I stopped working on schistosomiasis, it was renamed CAA [circulating anodic antigen]. Almost nobody knows that I worked on this antigen. It was developed about five or six years after I defined what it was.

Andre Deelder [Dr. André M. Deelder] in Amsterdam started working on it. He got the edge on me. He developed the monoclonal antibody to the antigen. He developed a very sensitive assay for detecting it. That assay became the basis of commercial tests that are now used experimentally, are now used to define, to diagnose, and to quantify infections.

There was also another competitor, Yves Carlier [Dr. Yves Carlier], who was working in the Institut Pasteur. He was working on cathodic antigen. I was working on an anodic antigen. This led to two types of assays. Subsequently the positive antigen developed recognized by Carlier was developed as a commercial point of use assay to diagnose schistosomiasis in the field. More recently investigators from the same group develop a more sensitive assay using the antigen that I worked on—CAA--and developed an even more sensitive point of use assay. I developed an assay for antibody, not antigen.

At that time, there was an IFA [Immunofluorescence Assay] test for lupus, in which you took fixed cells and layered patient sera over them and looked for the presence and reactivity to the cells' DNA. I knew at this point that the schistosomiasis antigen was in the gut. I said, "Well, let me just look at the gut and see this florescence." By that time, I knew that I could use a carbohydrate fixative. It was called Roseman's fixative. I sliced these worms and I did an indirect IFA. You put the patient serum on the worm sections and determined if antibodies in the patient's sera bound to the worm gut using indirect immunofluorescence. If antibodies bound the gut it indicated they were exposure to the parasite and were likely infected or previously infected. It turned out that these guts lit up like neon signs. It was very sensitive, so I did a blinded assay of all the patients that I had, and I found out it was 100% sensitive and 100% specific. It was a great assay. Shortly after that, Franz von Lichtenberg, who was a big wig at WHO [World Health Organization], wanted to compare all the assays that people were doing. We validated this assay with quantification of the stool. The quantification of the stool was being done nowhere else in the world. In schistosomes, there are not a lot of eggs that are excreted; 500 eggs per gram is considered a very heavy infection. The normal stool exam at a lab would be 20 eggs per gram. That's the limit of what you could see if you just sent a sample to a standard lab. With my assay, we were able to identify one egg per 100 grams of sample.

Harden: Wow.

Nash: Okay? One egg per 100 grams versus 20 eggs per gram. We knew that at one egg per 100 grams, patients were still serologically positive. It was the perfect test for somebody who was exposed to very small numbers of worms. In the validation studies conducted by WHO, however, they came up with a lot of false positives, but they had not validated their sera correctly. They were doing it wrong. The test that I had developed was correct. It was a very sensitive test. Subsequently my test never caught on, except in a few places that actually used it. That was in Amsterdam and in Sweden where they still use it for screening patients--travelers, for instance, where they have very high titered antibodies, despite the fact that you have very low worm.

Harden: In 1982, when you published your review article about schistosomiasis, FDA [U.S. Food and Drug Administration] approval of the drug that treats it, Praziquantel, was imminent but not yet finalized. You and Allen Cheever conducted the double blinded study that demonstrated its efficacy. Would you walk me through this?

Nash: Yes. It's a more complicated story. While I was away at Harvard, there was another guy who was a major player whom I didn't mention, Eric Ottesen [Dr. Eric A. Ottesen], who got his MD at Harvard. He was a year behind me. He also went to Duke. He was a pediatrician. Eric became the head of the filaria lab. He was very successful and still is very successful. He became aware of a family of schistosome infected patients who came to the Clinical Center. These patients were infected with *Schistosoma mekongi*. It is a different schistosome species that lives in some areas of the Mekong river. At this time, Cambodia was having a big problem with the Khmer Rouge, and people were fleeing, so there were a lot of refugees. The patient group was an extended family that had been diagnosed with *S. mekongi*, a close relative of *S. japonicum* which is treated with a very toxic experimental drug call tarter emetic.

At that same time, Bayer had developed Praziquantel. There were studies that had been done all over the world. The upshot of those studies was that Praziquantel was a fantastic drug. It was given by mouth, which was a plus because most drugs were given parenterally. It was very safe, and it had great cure rates. There was nothing wrong with this drug. The only problem was that it wasn't available in the United States because there had been no clinical trial here.

I made arrangements to use this drug to treat these patients, in conjunction with Eric and Allen Cheever. I went over to the FDA, and there was a guy there who did parasitic disease drugs. His name was Edgar Martin [Dr. Edgar Martin]. Edgar was an old-time Belgian physician who had spent time in the Congo and knew a lot about tropical diseases. Bayer was very anxious to get approval for Praziquantel. At that time, the required clinical trial had to be done by an American investigator, which was really hard to do, because there was very little schisto in the United States. How could you do a really proper study?

The arrival of this extended family with *Schistosoma mekongi* was an opportunity for Bayer and an opportunity for us. I devised this double blind, randomized, crossover trial. I think we had 16, 15--I can't remember exactly how many patients. We brought them to the Clinical Center and divided them in half. I was the blinded person. Eric was the person who gave the real drug or placebo and could assess if the patients needs special treatment, and I was the assessor for side effects At one point, they all got this drug, and I went around to see what their side effects were and marking them down. We did all the stool exams before and after. It was a very successful study. A paper came out describing both the efficacy of the drug to *Schistosoma mekongi* and its toxicity. We treated all the patient successfully with limited side effects and this study allowed the FDA to approve the drug. It was a really great study. It cost nothing to do. Nowadays you couldn't do it in a year, and you'd probably spend two or three million dollars doing it.

Harden: Before we stop for this first session--and I think we'll stop before we move on into your work on *Giardia*--I have one more thing that I want you to tell me about. It's the development of the method to use ultrasonography to diagnose Symmers' fibrosis.

Nash: That gets back to Allen Cheever. Allen Cheever was a liver pathologist. There were three in schisto at the time. Franz von Lichtenberg, who was a wonderful guy and was at Harvard when he was a pathologist. Allen Cheever, who trained at Mt. Sinai as a pathologist when there was a famous liver pathologist there. Finally, there was one in Brazil. Zilton Andrade [Dr. Zilton A. Andrade] who's still living. He's the only one living. He's very old, but he's very, very good.

At the center of intestinal schistosomiasis pathophysiology was a peculiar liver disease, described by a guy by the name of Symmers, S-Y-M-M-E-R-S', not apostrophe S. If you use apostrophe S, you know you never read the original paper. There are a lot of people who didn't. The condition was called Symmers' Pipestem Fibrosis. It was Symmers' Fibrosis or, what I think it's mostly called now, periportal fibrosis. This condition occurs at the end-stage of the disease. If you developed it, you had a good chance of bleeding and dying. The way you made the diagnosis was by doing a wedge biopsy of the liver. This was a surgery to open up the patient and do a wedge biopsy. This fibrosis is a macroscopic fibrosis. In other words, if you cut the liver, you see these bands, these thick bands of collagen tissue that mark the liver in a very specific way in the portal tracts. The reason wedge biopsy surgery is required is that one could not easily cut the thick bands of collagen and the sampling of the liver would be not be indicative of the true diagnosis. Cheever had done some work in Egypt. He stayed there for two years doing some very classic pathology on schistosomes in Egypt, which is the home of the bad schisto. He went back for a meeting. When he came back, he told me about a paper that was presented by Mohamed Farid Abdel-Wahab [Dr. Mohamed Farid Abdel-Wahab]. This guy actually lived in the same building that I did when I lived in Rockville. He was teaching at Howard [Howard University College of Medicine]. He went back to Cairo. He had published a paper in a book of abstracts or descriptions of the presentations of the meeting. In one of the abstracts, he described using ultrasound to diagnose what he thought was Symmers. Well, nobody read it, because it was published in an obscure journal. It wasn't even a journal, a proceedings document. It was not a great study, because it had no controls. It had nothing that you could say was really true, but we thought that clearly there was something to it.

When the patients came to the Clinical Center with *Schistosoma mekongi*, we did ultrasounds on them, liver ultrasounds. Lo and behold, you could see the fibrosis that was described in the Egyptian abstract. It was like you cut the liver in front of you. It was so dramatic. There was no way to do this study. I had gone to Egypt and talked to the author of it and said, "Let's do a study doing this." Well, Egypt is an impossible place to work. One university hated the other one. Then there was the issue of the place--the site was controlled by one group. Another group did the ultrasounds. Another group would do something else, and they'd kill each other before they'd work together. I couldn't really do anything in Egypt.

Meanwhile, a guy by the name of Jim Bennett [Dr. James Leroy Bennett], whom I knew, a neuro-physiologist trained in parasitology at Hopkins [Johns Hopkins University School of Medicine], had gotten a grant or funding to study parasite diseases/tropical diseases in Sudan and Khartoum. One day Jim was visiting, and he said to me, "Do you have any ideas about doing a study?" So having been thwarted in Egypt, I was definitely interested in finding a way to do the ultrasound study. I told him about this, and Jim is a wonderful guy. He's brilliant. He's not a clinician, but he's brilliant. He had already identified Mamoun Homeida [Dr. Mamoun Homeida] in Sudan, who was a liver expert, a GI [gastro-intestinal] expert who was trained in England but had come back to Khartoum. We decided, that if we trained him to do ultrasonography, he could do this study. Actually, we brought him to NIH, and he was trained in ultrasonography at the Clinical Center to do this study.

Right after that was published, the use of ultrasounds became the standard of care. Mamoun Homeida, the guy in Sudan—very smart guy, a very effective person--started looking at villages with the idea of using this technique to get the history of Symmers' fibrosis--when it develops, who develops it, and so forth, which he did in many villages. Then he treated Symmers' patients with Praziquantel, and he saw whether Symmers' fibrosis went away or not. This was ground-breaking stuff and now is the standard in the field. That is probably the most quoted paper that I did. I'm the last of a whole series of authors, and nobody even knows I ever did the paper.

Harden: You were the senior author.

Nash: Yes, I was the senior author, but they usually say "et al." after the first few, so the "et al." edits me out. But that was really a very nice study. It was funded by the Edna McConnell Clark Foundation. The Clark Foundation, unbeknownst to almost everybody, was funding tropical medicine. It was funding some social work in New York and also tropical medicine. They actually had a lot to do with the early development of schisto . . . . Schistosomiasis was the first parasitic disease studied in the modern era. Previously, it had all been about malaria. It was the first time that somebody paid attention to schistosomiasis, put money into it to develop people who became interested in it. That was the impetus for parasitology to become something more than a descriptive discipline. It was the first time that big league immunologists became involved.

It took another 10 or 15 years, but parasitology became a field of study using modern methods answering complex questions about how the organisms lived and caused disease rather. It became a model for how organisms adapted to live. It started with that funding and with another guy by the name of Ken Warren [Dr. Kenneth S. Warren]. Ken Warren was another person who trained in LPD in the schisto section, and he started a schisto section at Case Western [Case Western Reserve University]. He became a prominent proselytizer for tropical medicine and an important person in developing parasitology. Then he went on to Rockefeller to develop the discipline even further.

This is Part Two of the oral history with Dr. Theodore Nash on October 1st, 2018, at the National Institutes of Health about his career in the National Institute of Allergy and Infectious Diseases.

Harden: Dr. Nash, let's move to discussing the major line of research that occupied you for more than 20 years on the protozoan parasite *Giar dia lamblia.* Would you start by telling me about the parasite itself and about the disease it causes?

Nash: *Giardia* now goes by several names. But that's the old name and I keep it. Part of the work that we did showed that *Giardia* species are very different organisms. They looked the same, but many of them are quite different. *Giardia* was probably first described by van Leeuwenhoek in his own stools. The original description is hard to understand because he's describing something that has little feet that are moving. But in general, the people that tried to interpret what he said say that *Giardia* is what he was describing. In the mid 19th century, it was again described by Lambl [Dr. Vilem Lambl]. It is extremely common all over the world. And the prevalence of infection can be extremely high.

The old parasitologists didn't think that the organism caused much disease, although I think that there was some inkling during the Crimean War. But in the first World War, you could pick up papers where physicians describe a huge amount of organisms in the stools of patients who were ill. But still *Giardia* wasn't accepted as a cause of diarrhea, malnutrition, and sometimes even death. Even up until about 1967, '68 or so, it still wasn't accepted. There is a paper out of Boston where they're describing patients who are very ill, some of them even dying, with *Giardia,* but not accepting that it is the pathogen causing disease.

In 1969 there was a publication in the *New England Journal* describing an epidemic among visitors to Aspen, Colorado. *Giardia* was implicated definitively as the cause of that epidemic of diarrhea and GI upset. That outbreak was more or less the key to making medicine view *Giardia* as a pathogen. The old-timers still didn't believe it because most people with *Giardia* did not have diarrhea and they could not see an association between being infected with *Giard ia* and having diarrhea.

And even to this day, there's a dichotomy between the disease that occurs in countries or places that have fairly high standard of hygiene, where *Giardia* is not prevalent compared to places in Egypt where almost everybody has *Giardia* by the age of two yet few have disease that you could ascribe to the infection. That dichotomy is still a major question for medicine to explain.

Giardia has turned out to be a major cause of waterborne epidemics in the United States and was one of the reasons that water supply companies needed to filter their water instead of just adding chlorine. *Giardia* and a lot of other protozoa have cysts in their infectious stage that are not affected by the usual concentrations of chlorine in the water. This led to many epidemics of waterborne disease. *Giardia* was therefore the organism that caused most of the GI epidemic disease in the United States that was defined to that time. Nowadays, it's a minority for other reasons that we can go into.

At the point that water filtration became available, the amount of *Giardia* infection was lowered. At the same time *Cryptosporidium*, which was not even described yet--or it was described but not appreciated until it was described in HIV patients—forms a much smaller cyst. And it is much less efficient in being excluded from the water supply. Even more recently, an organism which is a fungus called Microsporidium is much smaller than either *Giardia* or *Cry ptosporidium* that requires other means to exclude it from the water supply.

Back to *Giardia* as a waterborne epidemic. It was common wherever fecal contamination occurred. Daycare centers often had prevalences of 70, 80%. It was a major problem for them. It was a problem for homosexuals--gays who had sex with men. It was a problem for travelers. It's still a problem in swimming pools because chlorination does not affect *Giardia* that gets into the pools or recreation areas because of fecal accidents. So it plays a role in diarrheal disease. It still plays a major role in the Third World where endemic infections are really common, yet it doesn't cause much disease. And that dichotomy raises the question: Why does *Giardia* cause disease in non-endemic populations and very little disease in endemic populations?

Harden: Let's talk about your research on this organism. You began by building on the work of Louis “Buddy” Diamond and David Keister [Dr. David Keister], who developed a medium that's now used to culture *Giardia*. Tell me about your research isolating and characterizing the different strains that establish the principle that it isolates different?

Nash: The impetus for doing work on *Giardia* for me personally started when I was doing a fellowship in Boston, where I came across a patient with nodule follicular hyperplasia, which is a particular type of process that's associated with *Giardia*. It is still not known why that occurs. And the problem was that it wasn't possible to culture *Giardia* axenically, that is alone. There was a guy working in the mid-70's called Gene Meyer [Dr. Eugene A. Meyer] who devised a very complicated medium for growing *Giardia*. He was the first person to axenize *Giardia* and grow it. However, he used human sera in the medium which added a complexity to making a medium that could be easily made and the same with each batch. Dave Keister in Buddy Diamond’s lab modified the medium they were using for *E. histoltica* for *Giardia* and that became the standard medium for *Giardia*. Using at first Meyer’s medium and then Keister’s we were to isolate the *Giardia* from a patient who became resistant to the usual drug, metronidazole. That organism, called WB became the protypic isolate and was the first to be fully sequenced. We devised a combined treatment regime for the patient that worked and it became the basis for treating difficult to cure patients. Even now it is the best regimen.

We were working with Dave Keister and another colleague, Fran Gillin [Dr. Frances Gillin], who was in Buddy Diamond's lab. She was working on *E. histolytica* and I convinced her to work on *Giardia*. She became a major *Giardia* investigator, and she didn’t work much on *histolytica* after that. She was the culture person for a long time. And then when she left NIH, we had to take it up and do isolation along with Dave Keister, who helped. But he wasn't directly involved. He developed a method to infect infant mice with cyst of *Giardia*. Almost all cyst infected the intestine of these mice and organisms purified from the mouse intestines were then used to establish axenized cultures.

So using both methods that Fran Gillin subsequently developed to isolate *Giardia cysts* in vitro and in vivo using baby mice, we were able to culture over 25 isolates. The problem was identifying them. I had an inkling that they were different because of the patterns that we found labeling their surface with radioactive iodine. By that time, I had a fellow named Phil Smith [Dr. Phillip D. Smith], who was the first person in my lab to work on *Giardia.* As he began working on *Giardia,* he had some technical problems, and subsequently I surface radiolabelled *Giardia* using the same method I used to label GASP and started to study the surface proteins of *Giardia*. There were some differences in the surfaces and we asked how this was occurring. I developed a specific antisera to a whole series of *Giardia.* I looked at the surfaces of these organisms and their secretory antigens. Eventually, I devised a number of ways of telling them apart. When molecular biology came, I devised a system for telling them apart, using RFLP (restriction fragment length polymorphisms). That was one of the first times that anyone used DNA from a eukaryotic organism. In this technique, you take the DNA and digest it with enzymes. You get a pattern. But the problem with a complicated organism is that you don't see a pattern like you do with viruses, for instance, that have very small genomes. You just see a smear. And so we had to get a probe in order to locate specific DNA digestion differences.

Molecular biology was first getting started, and our molecular biology data lab was headed by a guy by the name of McCutchan [Dr. Thomas McCutchan]. Along with John Dame [Dr. John B. Dame], one of McCutchan's fellows, we made a genomic library and used pieces of specific DNA in the library to see if they could recognized unique patterns among the different *Giardia* strains whose DNA was cut with different enzymes. And we eventually found a number that did detect differences between some isolates. Subsequently using that technique we grouped these organisms. The paper that we published in JID about '85 that showed that they fell into three groups. Now, it was sort of interesting what happened after that.

That was about three or four, maybe even five years before anybody else started working on methods to differentiate *Giardia*. When other people started doing this, I had stopped working on it because it had become boring to me. Other people started working on it and renamed the group names, greatly expanded the number of organisms, and also renamed the system although it was absolutely correct. Nowadays, they don't even reference this groundbreaking work. It's lost in the literature. It's a disaster.

The other reason that we were trying to tell one *Giardia* species from the other was that the water epidemics were associated with beavers. Beavers in various waterways were fecally contaminating reservoirs. The question was whether the beaver was carrying its own species of *Giardia*, or was it a human *Giardia*? It turned out that they didn't have their own separate species. They had one that was also found in humans. It's likely that beavers are infected by human feces in the waters they inhabit, and then they contaminate the reservoirs.

Harden: This is a fascinating line of research. Would you talk just one more minute about the differences in endemic and non-endemic or epidemic populations?

Nash: There are a lot of things about the clinical course of giardiasis that we don't understand. We'll get into an antigenic variation I think a little later. But *Giardia* differ. And so the question is, why do some people who get infected get sick and some don't? No one has the answer to that, but it is well established that the microbiome has a large effect to hinder or allow Giardia infection in animals. I did experimental infections in humans to prove Koch's postulates via an NIH contract at the University of Maryland. We also proved at the same time that antigenic variation occurs in experimental infections in humans. And only half of those patients got sick. They all became infected, but only half became sick. We still don't understand why. More recently, there was a major study done all over the world, looking for causes of diarrhea in children. In that study, they couldn't show that *Giardia* caused disease. There was another study that came after it by another group that suggested that *Giardia* did cause certain types of disease. It's still open to question about what's going on. In general, the literature is quite mixed about whether *Giardia* causes disease in endemic areas

And I would say right now that there are very few data suggesting that it causes disease in endemic areas. This is in plain contradistinction to what happens in the United States or other developed areas where there are sometimes huge epidemics. Whole cities almost are infected. Current data show that *Giardia* causes irritable bowel-like symptoms post-*Giardia* infection, which also happens after GI infection with other organisms.

Harden: You have developed vectors and techniques to transfect *Giardia* and use them to find the structure and character of specific genes. Do you want to talk some about that as well as what you did with the process of encystication? And the transport within cells—I found that fascinating.

Nash: Before we talk about that, let me talk about one other major thing. After we found that the surfaces of *Giardia* differed, then the question was: Why and how do they differ? Using a panel of monoconal antibodies were found that the surface of *Giardia* changes. Over years we showed that this was a programmed change using about 200 related surface proteins that changed over time called surface antigen variation. It turned out that some of these monoclonals killed the organisms and this allowed us to study the nature of antigen variation and to characterize the variant proteins themselves. We developed a method for easily cloning *Giardia.* Then we were able to add antibody to the clone that reacted with almost all the organisms. We were able to show that almost all of the organisms died except a few that survived. And these organisms were expressing new surface antigens. And we repeated that several times making more monoclonals.

So it turned out that we have a library of surface antigens. We called them VSPs, Variant Specific Proteins. Using these antibodies, their ability to produce clones, and the cidal activity of the monoclonal antibodies, we were able to answer questions. What is its purpose? How is it doing it? What is the biological significance? A lot of these are not actually even answered yet. But the usual--at least very glib--answer is for antigenic escape. Now, that's where Steve Singer's [Dr. Steven Singer] paper comes in.

I had developed a body of literature, a body of experiments showing that not only were these organisms expressing different surface antigens, but that they differed in fundamental biiolgoical ways. One of the things we did is to add normal proteases from the gut of a human—trypsin, for instance, and chymotrypsin. When we added them to these organisms, they did the same thing that monoclonals did. You've killed all the organisms except a few that survived. This demonstrated that there was a biochemical difference in what each surface antigen did. Some of them were resistant and some them were not. This suggested that the surface antigens were not different in order to escape the immune system. They were biologically significant. Some of them were able to survive in the bowel in the presence of proteases. And some of them were not. This meant that one organism, which was expressing a variable surface antigen that was resistant to the proteases or gut environment, would be able to multiply and infect the host. On the other hand, if the organism was sensitive to the host's proteases or environment, either the organism had to change it surface to a better surface antigen or not survive. This process was independent of the adaptive immune system.

So I called this biological selection. I spent a whole summer making monoclonals to this organism that went into mice, adult mice. Using those monoclonals, we were able to track what surface antigens these organisms were expressing. And using SCID [severe combined immune deficiency] mice and comparing them with normal mice, we were able to show that despite the fact the SCID mice had no immune system, *Giardia* changed what surface antigen covered their surface and allowed the surface antigen to survive or change. We showed that the same type of process occurred in different animals, but the surface variant proteins that allowed survival in one animal were not the same for each animal. In particular, irradiated gerbils, animals that had no adaptive immune system comparable to SCID mice, selected for *Giardia* that had different resistant surface antigens compared to the mouse. Normal mice developed a good immune response to anything that you put in them and eliminated the organism almost totally. Not quite totally. This was in comparison to the SCID mice or irradiated hamsters. Gerbils that accepted certain proteases, certain antigenic variants and didn't allow others.

This proved that there was biological importance. That experiment was only allowed because there was another person in my lab, a fellow, Linda Byrd [Dr. Linda G. Byrd]. We had developed a model system in adult mice for *Giardia*. I did the preliminary experiments showing that only one of the 25 isolates could go into adult mice and cause a viable infection. That was the organism that we were able to use in Steve Singer's experiment.

In trying to do some of these experiments, we came across a problem. You couldn't duplicate the experiment in SCID mice. Now, SCID mice would normally be infected with most strains of *Giardia* you put into them. They grow very well. They grow better than, of course, in an immune mouse. But we found in one very large and complicated experiment using these SCID mice that we readily infected a few weeks before, we couldn't infect most of the supposed same mice again.

Steve, very astutely--this was almost all his own work--was able to show that this was due to the flora of an animal. As I said, one of the suppliers sprayed the mice with a particular flora, a defined flora. And these mice actually became resistant to *Giardia*. And so he did the definitive experiment. When he got rid of that flora, the SCID mice were now susceptible. And when he put back the flora they were again resistant. It was one of the first examples demonstrating that microflora affected organisms. It was, again, forgotten in the literature. It's almost never quoted. If it's not the first, it's very close to the first.

By the late 80's, '88 or so, we had a person, Michael Mowatt [Dr. Michael R. Mowatt], who came in from Rockefeller. He had been working on another protozoa, a trypanosome. He brought good molecular biology into the lab. He was leading the charge in developing vectors. There were also several other people important in that effort, including Heidi Elmendorf [Dr. Heidi E. Elmendorf], who was married at that time to Steve Singer, and Janet Yee [Dr. Janet Yee]. Janet Yee first developed a vector better defined by Steve. And then Heidi and another person, Sara Davis [Dr. Sara R. Davis], started doing transcription promoter bashing, trying to find out which promoter would work in *Giardia*.

All of this work was answering questions about the basic molecular biology of *Giardia*. What kind of promoters they had, how long they were, how big they were, what they did. We did original work that allowed us to make efficient vectors or reasonable vectors. They weren't actually that easy to use because the promoters were so small that you had to use only very specific cuts and very specific enzymes. And if they didn't have that enzyme or that cut, you had to do some manipulations which were a little tricky.

But anyway, we developed vectors that we could put in a gene. Most of them influenced the variant surface proteins, but we could also make them for any other gene you want. That brought in the era of using the vectors to study cellular processes. And that, in turn, brought us into studying vesicular transport. Fran Gillin had done some very nice work in encystation. She showed that *Giardia* were very unique and they possess something called encystation specific vesicles.

And so when you started to encyst *Giardia* in vitro, they went through the developmental process that changes the whole organism from a motile trophozoite animal in the bowel to a resistant form called a cyst. This transformation was very complex for the organism. And there has been a lot of work using it as a model system for developmental biology and also vesicular transport. It turned out that *Giardia* do not have a Golgi apparatus. So the question came up, “How does Giardia transport proteins without a Golgi apparatus?”

Harden: Would you define Golgi apparatus?

Nash: In vesicular transport in mammalian systems or a higher organ systems, there's a regulated transport system. Proteins are made in the endoplasmic reticulum, and then they are transferred by vesicular transport to the Golgi apparatus where they're transported to different target areas in the cell such as the outer membranes or other organelles. So it's a very sophisticated system for taking cargo that is made by the cell and transporting to its specific location within or for secretion outside the cell.

Harden: Within the cell?

Nash: Within the cell. So *Giardia* didn't have a Golgi, which raised the question, “How did they perform vesicular transport, which is present in all eukaryote cells without a Golgi?” A lot of people were working on that, using variant surface proteins, which were constituently exported to the surface and comparing them to encystment proteins, proteins that went into the cyst wall and all those proteins that allowed the cyst to exist.

We did some of the first studies using some cyst wall proteins that were defined by others. We used a protein called cyst wall protein 1. and we defined cyst wall protein 2. And then another cyst wall protein 3 was defined later by Fran's group. And all of these proteins can be used as markers for following the process of encystation and following changes in vesicular transport. Other people studied transport in *Giardia* using these proteins and systems really did some very fine work with it.

Harden: So anything else we should cover with *Giardia* before we move on to neurocysticercosis?

Nash: Oh, let's see. We did do the human experimental infections. We were getting the tools that would enable us to infect and study humans. This took a long time because of the regulatory IRB [Institutional Review Board] hurdles that we had to go through. But it turns out that some *Giar dia* were infective for people and some not, even though they came from people originally. We were able to infect humans and follow them for 21 days. Some of them got sick and some didn't. And that fulfilled Koch's postulates. We did all the things that you're supposed to do to fulfill Koch's postulates.

Another thing is that we infected them in later experiments, human experiments. We were using clones, and we were using those monoclonals that we had previously made to look at the surface. We're able to analyze organisms that were present in the duodenum of humans and also in their stool, and to show that the organisms’ surface antigens changed over the course of infection. We were able to show the timing of that. Now, that was only to day 21, so we don't really know what happens after that. So *Giardia* infections can be very long-lived. But we were unable to define what was going on in humans over a long period.

There was only one other study done in humans in *Giardia*. Well, one reasonable study. There were a few studies in the literature that didn't really count very much. But those were done very early. And that other study was done in prisoner volunteers. It was an early NIH study done in Tennessee in prisoner volunteers. They used cysts that they isolated. And they gave a graded number of cysts to volunteers. An they showed that it only took 10 cysts to infect a hundred percent--

Harden: Wow.

Nash: Of the volunteers. And this is a very small number of cysts considering that you can have 10 million cysts per gram of stool.

Harden: Wow.

Nash: And so it only takes a little contamination to become infected.

Harden: Let's turn now to your work on neurocysticercosis, which began about 1985. And for this work you did at least one study in Peru. But to get us started, once again, would you briefly explain what we're talking about with neurocysticercosis?

Nash: Well, neurocysticercosis is a fun disease. And before 1975 or '76, there was a large literature, of course, old literature. It started around 1850 when the lifecycles of cestodes were defined. And shortly thereafter the lifecycle of *Taenia solium*, the pork tapeworm, was defined. The disease neurocysticercosis was well-described by the late 19th century. There's a very nice pathology article in German in the early 1900's--1915 or so--by Henneberg [Dr. R. Henneberg] in the *Handbook of Neurology* that describes almost everything you wanted to know about cysticercosis, all the complications.

The next advance of neurocysticercosis was the recognition by MacArthur [Sir William Porter MacArthur] in 1933 that seizures were common in English servicemen returning from a tour in India and that the cause was due to neurocysticercosis. Taking advantage of a similar cohort of returning servicemen Dixon and Lipscomb [Dr. Henry Brian Frost Dixon and Dr. F. M. Lipscomb] defined the epidemiology and symptoms that were usually caused by NCC [neurocysticercosis]. These servicemen were followed for decades and this landmark paper was published in 1961. They established that seizures were a common manifestation of neurocysticercosis. That paper defined that seizures were really common in patients. And they even defined the timing of the seizures, just from their clinical observations. They were not using sophisticated imaging that we have now. They were just using X-rays. They were able to define this disease via biopsies and looking at calcification of the lesions.

That's where things stood and up until the early 1980's. By then, CT [Computed Tomography] scans came into existence, and at the same time Victor Tsang [Dr. Victor C. W. Tsang] at the CDC developed a good serology. And about that time Praziquantel became available. So you had Praziquantel, with which you could treat cysticercosis, you had CT scans with which you could diagnose it, and you had a serology that you could use to confirm it. So this all came about very quickly and people were diagnosing by imaging and treating this disease using these modalities. This is how they were defining cysticercosis in the modern era. It could be treated with Praziquantel to some degree or another, but you needed steroids in addition because when you killed these parasites, they released antigen that caused a huge amount of inflammation and caused some patients to die.

All of this was very empiric, not studied rigorously. Nobody knew exactly how much drug to use, how much steroids, how long to treat it, what happened in the long run in these patients. Because I had learned a great deal about Praziquantel, I became interested in cysticercosis. And my boss Frank Neva and I had been following the literature closely. I had reviewed a paper by Sotelo [Dr. Julio Sotelo] in the *New England Journal*, and the *Journal* asked Frank, who then asked me join him in writing a review of neurocysticercosis that was published in the *New England Journal* in 1984.

That was the impetus for me to start a program on neurocysticercosis. And he decided that we were going to go to Mexico City where all these investigators were to find out what they were doing and what the dope was. So we went there and visited their interesting program. They were almost the only persons in the world at that time who were doing any decent work. There were a few other papers. There were some Indian papers that were coming out. There were some papers from Korea. But the Mexicans were really doing the heavy lifting when it came to cysticercosis.

So from about 1985 to about 2000, I treated patients and learned how to treat them. My first patient was in '85. She happened to be an ambassador who got infected and had started to have seizures. She had a calcification that had edema around it. That same year—1985—marked the first time that MRIs [Magnetic Resonance Imaging] became available. NIH had one of the first MRI machines. I knew that I couldn't compete with the Mexicans and others who had all these patients that could be studied to develop treatments, but I did think I could find out why they were having seizures. And so every time a patient had a seizure I would do an MRI as soon as I could. What I found during those 10 or 15 years is that some of the patients had calcifications with edema—inflammation--around them. This was heretical at the time. Nobody thought that calcification could induce inflammation and cause seizures. When I first saw it, I had no idea what it was. I didn't know whether I was reading the MRIs correctly or what was going on because nobody believed that a calcification, which was a dead parasite, could cause anything.

By 1999, we had enough data to show in a paper that the calcifications caused the edema. That it was repeated. In other words, in some people it happens repeatedly. And that the edema was associated with seizures. I felt this was really important. That opened up a series of investigations and studies that I did in collaboration in Peru with Hugo Garcia [Dr. Hector H. Garcia]. At that time, Hugo was getting his PhD and starting his program. I asked him to design a study on this. I told him about this process that was going on that I thought was really important. It had to be very common because I was seeing it at NIH, even though we didn't see that many patients. I believed it had to be very common everywhere else. So he devised a study to look at calcifications in people who had seizures. That study was groundbreaking because it showed that of people who had seizures and calcifications, half had edema associated with them. Subsequently, we did a PET [Positron Emission Tomography] scan study with investigators here (Fujita [Dr. M. Fujita] et al in Bob Innis's group [Dr. Robert Innis]) to show that microglial activation mediated the inflammatory response. It was more or less taken as proof that the edema was an inflammation related to the calcifications.

Among patients who have calcifications and seizures--and many of them live in villages in endemic areas—half of the seizures are associated with this edema and half of them are not. An important part of this finding it is that you could probably treat this situation with anti-inflammatory drugs rather than an anti-seizure drug. It's likely that you can prevent this and it's likely that you can treat it in a very specific way, very differently from the way it was currently being handled.

The other major thing that I was very interested in was this inflammation. People knew that there was inflammation, and if they had read the German article in 1915, there was no question that the inflammation was really important, and yet it wasn't being treated even though the inflammation is what kills people. It is what causes almost all the disease in neurocysticercosis. I popularized that idea and that physicians needed to pay attention to inflammation. We did a study comparing the use of a little bit of steroids to a lot of steroids. We showed that by using steroids, patient seizures were decreasing. Previously, nobody had ever shown that steroids were needed in neurocysticercosis. There were no randomized studies. Nobody knows how to use steroids. Nobody knows how you use steroid-sparing agents or other agents in order to inhibit this inflammation. This is because steroids are bad news in the long run. They have lots of side effects. You really need to protect the patient. And actually, today I just submitted a paper about our experience using Etanercept (now published in the *American Journal of Tropical Medicine and Hygiene*), which presents a series of cases, but not a randomized trial. Basically, we think it works pretty well.

So those are the two major things that I think I contributed to the study of neurocysticercosis.

In Peru I also set up a program with Hugo Garcia to study neurocysticercosis in pigs as a model for human neurocysticercosis. We formed a group and have been able to show in vitro drug sensitivities to *Taenia solium*. We also developed a pig model for brain studies. The pig model became the important thing there, as we were using Evans Blue to show blood-brain barrier of leakage and define certain cysts. We were able to show that these cysts were different from cysts that were not affected and had a huge amount of inflammation and that they were very pro-inflammatory. And then we used Etanercept in pigs to show that it inhibited all of those inflammatory side effects.

Harden: Let me step sideways for one question. The kind of work you're talking about has kept your patients alive when they were suffering from these seizures. Would you reflect on the need for this kind of work, especially in terms of your ability to do it here in the Clinical Center and in collaboration with people, say, in Peru? Given the lack of strong funding for this kind of work, could you do it anywhere else, such as at a university?

Nash: You can think of this as the glass half full or half empty. So from the half full point of view, I was able to take a subject that didn't exist and to make a big program out of it. Now this is the most common parasitic disease we see here at the Clinical Center. It is really important because of the migrant population that we take care. Because nobody really wants to deal with them or knows how to deal with them. It's expensive to treat them and the know-how is not very well disseminated. So we treat them very well, and we use them to try to define what makes good treatment, how to make the treatments better and how to diagnose the disease better.

The half empty part is that there was no extra funding to develop a program in the usual way that NIH develops a program. Normally, you would have a lab, and you would have funding for people to work in the lab. This was not provided. As a matter of fact, the funding for the Peru lab that I mentioned earlier that was quite productive was eliminated totally when other programs were not.

Although we learned a lot and we became proficient in treating and helping patients, it was very difficult to get anywhere on a more basic scientific level. And furthermore, the people with whom you could collaborate had their own things to do and didn't want to collaborate. They had better things to do. We were left on our own trying to figure out what to do and how to do it. We got good help from the Clinical Center staff, who have preformed and interpreted the imaging required to treat these patients over the years as well as performing lumbar punctures. We got some help from the people doing PET scanning. Of course, they developed the ligand and together we did a good PET scan study. And so there was some help.

But I think in general, there is no recognition that this is a prototypic inflammatory condition of the brain. And it can't be studied very well to understand the genesis of seizures. So how do people develop seizures? So this is actually a great model for studying how people develop epilepsy. With NIH funding, I organized a meeting to consider the question of how neurocysticercosis can be used to answer more basic questions involving the brain and the development of seizures. We wrote a paper on it, an editorial in *Epilepsia*. People read it and it went into one ear and out the other. Maybe one day it will be appreciated. But right now, it's latent. I think it's a goldmine for researchers.

Harden: There are definitely trends in science, and I'm sure there's a lot of jockeying for position among the different kinds of research. There is also the larger political issue of getting funding for tropical diseases in general from the Congress.

Nash: One of the problems with cysticercosis is the lifecycle of the causative organism and the complexity of the disease. The lifecycle cannot be maintained in vitro. The obligate carrier of the tapeworm is humans, and the tapeworm ova, the infectious ova, are excreted in the feces. They are what people ingest to get cysticercosis. So if you want to study this disease in an experimental way, you have to locate a person with a tapeworm. That means, essentially, that you have to be in an endemic area. The other problem is pigs. Most of the pigs in an endemic area are in areas where they have a viral hemorrhagic fever, Classical Swine Fever. There is an epidemic now going on if you're very current, both in Europe and in China. In Europe, they just found the disease in a few pigs, in wild hogs. But in China, it's about to decimate the pig industry. You can't import anything that comes from a pig into the United States, including cysticercosis, cysts. So that's always a problem, and it's a problem studying neurocysticercosis in the United States. But it's a problem studying it anywhere because the lifecycle is so hard and essential forms of the parasite so hard to obtain. So we get naturally infected pigs. And to get naturally infected pigs in Peru you have to basically have a team, a large team of people to identify the pigs, to get the pigs, to transport the pigs from one part of Peru to where the studies are being done. This requires an army of people. It is very labor-intensive, very expensive.

That's only one of the major impediments. The other is the fact that the disease is hard to treat and to analyze because it takes brain imaging. One of the major questions is how to study the disease in Africa? Africa has a huge amount of neurocysticercosis, which is more or less undefined. They have almost no imaging or very limited imaging. When a person comes in with a seizure or another brain symptom, it's very limited what you can do for them. Except for malaria, of course. Imaging is very hard to get, particularly MRI, which is available only in the big cities.

When we treat, we don't treat anybody without imaging because without imaging, you don't know what's going to happen. You don't know if they have a lot of disease or a little disease and whether they're likely to have seizures. How do you treat them with steroids when you can't image them? You don't know how much steroids to give. You don't know what you're doing. Funding agencies are not interested in eliminating cysticercosis because it's so difficult to study and so expensive to treat on an individual case. There are some efforts to diagnose it better, how to define bad disease versus not-so-bad disease. And there are some efforts to develop surrogates of imaging, surrogates of treatment, so on and so forth.

Harden: Let's move to the final major area of your research, leishmaniasis. Again, would you start with a description of what this disease is.

Nash: Leishmaniasis is the general name for different types of diseases caused by a group of organisms. There are different ways to divide the categories. Traditionally, there are two major dichotomies. The first one is where they're from. There are different species of *Leishmania* in the New World and in the Old World. The Old World species were defined and studied earlier. The Old World species come in two varieties, skin varieties that are mostly related that infect the skin and are limited to the skin. The other one is a visceral leishmaniasis. Visceral leishmaniasis is the one that was first defined. It causes severe disease, a lethal disease if untreated. In the early literature—let's say *Fevers of the Tropics* by Leonard Rogers [Sir Leonard Rogers],who worked in India for about two decades as I recall—you will read about epidemics of leishmaniasis going up and down certain valleys in India where millions of people were killed or died because of this.

Most of the focus of the world is on this lethal disease. How do you prevent it? How do you treat it? And what's actually going on? Visceral leishmaniasis is for the most part limited to two varieties. Visceral *Leishmania donovani* and *Leishmania infantum*. *Donovani* is the one in India and also in Africa to some degree. *Infantum* is present around the Mediterranean and mostly infects children, small children rather than older children. But it can also infect adults. It was brought to the New World and was thought to be a different organism, called *Leishmania chagasi* in the New world. But it's actually the same organism as *infantum*, somewhat mutated now that they've been separated for a while. It causes visceral disease in certain parts of Central and South America.

The cutaneous disease in the Old World is caused by a whole series of organisms, but mostly *Leishmania major*, *Leishmania tropica*, and *Leishmania aethiopica*, although now a whole series of new ones is being defined by molecular means. I'm not quite sure where that speciation is today. But the major ones are the ones that I've already mentioned.

The Old World leishmania are different from the ones in the Americas. The Central and South America organisms comprise a series of species that go from Mexico--and actually some in the United States--down through most of South America, excluding more or less Chile and Argentina. These come in a number of varieties. But the major difference is that they're harder to treat than Old World species. Some of them go to the mucosa of the nose and mouth. They can cause destructive lesions on the upper airway. One Old World species, *Leishmania aethiopica*, also does that. But it's lesser well-known and studied organism of the Old World. The major difference between those in the Old World and those in the Americas is that some of them go to the nose and the mouth. Another difference is that New World leishmania are evolving very rapidly. They're enzootic infections. For some of them, humans serve as a host, which a sand fly bites and then bites another human and transfers the organisms. *Leishmania tropica* is one example. They are called anthroponotic. But most leishmania infections come via an animal host.

Leishmania causing skin infections are really common organisms. It's a pain for people, and it can sometimes be very dangerous. If it goes to the nose it's really bad news. But in some areas of the world, like the Middle East, it's a common benign infection. People just get it and then get over it. It causes a scarring lesion that people for hundreds of years have known about. Many people tried protect themselves by immunization. There is a high degree of immunity to the infecting strain For instance, if they knew they had it, they would inoculate their daughters on some unseen area of the skin because they didn't want their daughters to scar on their face. It's a scarring disease that can be somewhat disfiguring.

Harden: Tell me about when you took over responsibility for research on leishmaniasis when Frank Neva retired and also about your work to substitute a new therapy for the standard therapy.

Nash: Well, you know, there are people who spend their lives doing leishmania research. And I have not done much research except for clinical research. We have labs that actually study leishmania, the organisms, and they have done very nice, groundbreaking work. My job was basically to take care of the patients that came in. Frank Neva did that for 26 years, the whole time that he was here. He loved that organism, he worked on it. He worked on it his entire career in parasitology. He taught me many of the ins and outs of patient care for leishmaniasis.

My contribution had to do with therapeutic drugs for the disease. For decades, the therapeutic drug of choice had been antimoniate compounds. Antimony is a heavy metal. These drugs come in different varieties in different parts of the world. Initially it was given IM [intramuscular injection] and then people started giving it IV [intravenous injection]. And nowadays it was given 20 doses IV. It really is a very toxic drug. I watched Frank give it to I don't know how many people--a hundred or 120 people--a good number of people. I've seen every complication except death from this drug. To me, the number and severity of complications made it just impossible. So I vowed not to use the drug. My contribution had to do with the use of a drug called AmBisome. The drug amphotericin was used for severe mucosal disease in South American leishmaniasis, but there was never a randomized trial. There was a series of cases showing that it was relatively effective. So when you couldn't use antimoniate or if people couldn't tolerate it, if it was too toxic or it didn't work, physicians began using amphotericin instead. Amphotericin is a drug that had been used for fungal diseases. We'd used it for decades. It had also been used for cancer patients who would get different systemic fungal diseases. It's a very toxic but different from the antimony drugs. There was no way that people would use it on a routine basis because it was just as toxic as the antimoniate compounds.

But AmBisome is a different formulation in micelles, in which a synthetic membrane of sorts encloses the drug in a small packet or micelle that contains a high concentration of drug so that much more drug can be given in a smaller volume and with fewer side effects. Having the drug packaged in micelles made it easier to give a much higher dosing in a shorter period of time. And this allowed the possible use of amphotericin in leishmaniasis. Some of the original work using AmBisome was done in India studying visceral disease, and it seemed to work really well. So then the question came up, “Can it be used in cutaneous disease?” I started to use it, and I found that it worked pretty well. Now, I don't know if I was the first person to use it or the second or whatever it is, but I certainly started using it very early.

A U.S. Army physician Alan Magill [Dr. Alan McGill], who was seeing a lot of leishmaniasis because of the wars in the Middle East published a paper that said that AmBisome didn't work. They had tried it on one person I think, and they published a paper. When I saw Alan, I told him, "This *is* really working." So he and his group developed a series very quickly to show that it worked and published it to my chagrin before I published my series. The other thing we popularized was using molecular biology techniques to diagnose and speciate the organism very quickly and then to pick the right drug to use. AmBisome was one of the drugs we used.

The other drug that we started to use very early was a drug called miltefosine. I used miltefosine experimentally, getting INDs [Investigational New Drug] on it from the FDA to use it in a number of patients. Eventually, we ran a small drug trial in conjunction with the company that produced it. We got a lot of experience using this drug. The advantage of this drug is that it's given orally. All the other drugs are parenteral, you have to give it IV, you have to get the patients to the hospital or put them in an outpatient setting to give them IV drugs. Now miltefosine is approved for use, but it is a very expensive regimen. We're now finding—this is unpublished yet—that it has a lot more toxicity than we originally believed. So it's not a great drug.

There is another series of drugs called azoles that we like to use. One of them is ketoconazole. There was a nice randomized control study showing that you can use it for certain American types of leishmaniasis. We always try and use that drug. It's a safe drug. It's an oral drug. So my contribution is a pragmatic one: How do you choose what drug to use? And how do you use these drugs appropriately?

Harden: I believe one of your postdocs, Jonathan Berman [Dr. Jonathan Berman], also worked with you on that. Would you talk a bit about him, in particular and in general about mentoring postdocs.

Nash: Actually, he was not my postdoc. Josh Berman was a fellow here in the 70's. When I came back in '76 from doing my studies at Harvard, he was here as a fellow of a guy by the name of Dave Wyler [Dr. David J. Wyler], who was one of the three clinical associates whom Frank Neva had hired (I was one of them) to take care of patients and to set up laboratories. There were Eric Ottesen [Dr. Eric A. Ottesen], myself, and Dave Wyler. And Dave Wyler was initially interested in malaria and later on got interested in leishmania.

I can't remember whether Josh was working with Dave exclusively and/or with Dennis Dwyer [Dr. Dennis Dwyer], who was our leishmania person who came from Rockefeller. Josh did his work in leishmania here at NIH, and then he went to the Army. There he did some seminal work in the drug treatment of leishmaniasis. Really nice work. He was very hard-nosed about doing good studies. Then he retired from the Army and began working for a company administering a trial for the drug company who sponsored the study we did. Josh was in charge of getting this drug through the FDA and getting all the data and so on and so forth. We were working with him to do that.

Harden: Let us finish up with your telling me about when you became famous in a book by Douglas Preston, *The Lost City of the Monkey God: A True Story*. Preston was a member of the exploration team looking for a lost Mayan city in Honduras and who praised you for treating his team for their infection with the leishmania causing the mucosal manifestation of leishmaniasis. I understand that you told him to take the halo off your head, but he didn't really want to. Would you tell me this story?

Nash: I was just doing what I've been always doing. And, you know, it's not appropriate for me to mention any of the patients' names except for Doug Preston. One member of that team contacted me through he American Ambassador in Rome where he was babysitting for the Ambassador's cat. He asked about where in the United States was the best place to be treated for leishmaniasis, and from that conversation, he became the first person I treated. Subsequently, just by word of mouth—everyone saying, "This seems to be a good place, and they know what they're doing,"—the others inquired about whether they fit into our protocol to evaluate and treat them, and most were able to come to NIH for treatment.

Most infectious disease physicians in the United States don't know anything about leishmaniasis. It's not common. Every once in a while a physician learns about it or is in a university that is in place where people get it or in big population center where they're likely to see some. But most physicians don't really understand it. It's a specialized disease, really.

At any rate, the members of the expedition came here, and I ended up taking care of them. At that time, miltefosine was not available, so they mostly got AmBisome. AmBisome had its usual side effects, some of which were nasty. I'd previously gotten into trouble using it, so I knew that you have to be very careful when using it. I think they all appreciated the attention that they got. But they got the same attention that anybody else gets here at the Clinical Center. They were not treated any differently. And of course, we didn't know that he was going to write a book about it. And I have to say that in quoting me, I don't know whether he was recording me, but he came damn close to exactly what I said. And, I mean, I don't remember word for word, but it was pretty good.

He appreciated the care. I'm still taking care of those patients, because they keep on relapsing. Their disease is caused by a new species of leishmania. It's not the same species that *braziliensis* is. *Leishmania braziliensis* is a group of organisms that's complex and that goes to the nose. One of the problems about the current speciation situation is that it doesn't reflect the diversity of the organisms. So *braziliensis* in Brazil, for instance, is very different from *braziliensis* in Bolivia. They behave differently. They react to drugs differently. The probability of causing nose disease is different. They have all sorts of differences.

And so it makes it very difficult to choose treatments because you have to know what the risks are. The risks differ depending on the geography, even though you're working with supposedly the same organism, the same species. These patients, although they were infected more or less at the same spot at the same time, manifested the disease very differently. Some of them had very little disease, little ulcers that self healed for some of them. But some of them developed just horrendous cutaneous involvement. I mean, huge amounts of skin. And they kept on relapsing. One of them in particular was very difficult. And eventually we got him cured by using miltefosine and AmBisome together. There's another person who has just relapsed for the third time. We're still trying to devise a therapy that will work for him. He has a lot of morbidities. We're limited in what we can do because he can get into big trouble just because of the drug toxicities. We're still working on that.

Harden: That brings us to the end of my questions. Is there anything else you'd like to get on the record before we stop?

Nash: I don't think so. We've mostly dealt with the science. There's a lot of political stuff that I didn't get into. I think for science, this record will be good enough. But every place has its political stuff.

Harden: Of course.

Nash: I've not been amused by a lot of it, put it that way.

Harden: Well, let me say thank you very much for these two excellent interviews.